



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Christian P. Larsen et al. **Examiner:** Not yet known
Serial No.: 10/057,288 **Group Art Unit:** 1646
Filed: January 25, 2002 **Docket No.:** D0136NP/30436.58USU
Title: METHODS OF INDUCING ORGAN TRANSPLANT TOLERANCE AND CORRECTING HEMOGLOBINOPATHIES

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CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on July 31, 2002.

Renato Marco P. Domingo
By: Renato Marco P. Domingo

INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b)(3))

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- U.S. Patent No. 4,603,102 issued July 29, 1986 – **Exhibit 1**
- U.S. Patent No. 5,430,057 issued July 4, 1995 – **Exhibit 2**
- U.S. Patent No. 5,434,131 issued July 18, 1995 – **Exhibit 3**
- U.S. Patent No. 5,559,148 issued September 24, 1996 – **Exhibit 4**
- U.S. Patent No. 5,637,481 issued June 10, 1997 – **Exhibit 5**
- U.S. Patent No. 5,773,253 issued June 30, 1998 – **Exhibit 6**
- U.S. Patent No. 5,844,095 issued December 1, 1998 – **Exhibit 7**
- U.S. Patent No. 5,851,795 issued December 22, 1998 – **Exhibit 8**
- U.S. Patent No. 5,876,692 issued March 2, 1999 – **Exhibit 9**
- U.S. Patent No. 5,885,579 issued March 23, 1999 – **Exhibit 10**
- U.S. Patent No. 5,885,796 issued March 23, 1999 – **Exhibit 11**

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- U.S. Patent No. 6,090,914 issued July 18, 2000 – **Exhibit 12**
- U.S. Patent No. 6,113,898 issued September 5, 2000 – **Exhibit 13**
- U.S. Patent No. 6,217,867 B1 issued April 17, 2001 – **Exhibit 14**
- International Publication No. WO96/23071 published August 1, 1996 – **Exhibit 15**
- Abrams, Judith R. et al., “Blockade of T Lymphocyte Costimulation with Cytotoxic T Lymphocyte-associated Antigen 4-Immunoglobulin (CTLA4Ig) Reverse the Cellular Pathology of Psoriatic plaques, Including the Activation of Keratinocytes, Dendritic Cells, and Endothelial Cells,” *Journal of Experimental Medicine*, 2000, 192:681-693 – **Exhibit 16**
- Adams, Andrew B. et al., “Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct Genetic Hemoglobinopathies with Minimal Myelosuppression,” *Journal of Immunology*, 2001, 167:1103-11 – **Exhibit 17**
- Ahmed, Rafi et al., “Selection of Genetic Variants of Lymphocytic Choriomeningitis Virus in Spleens of Persistently Infected Mice,” *Journal of Experimental Medicine*, 1984, 160:521-40 – **Exhibit 18**
- Andreasen, Susanne Ørding et al., “Surface marker abnormalities in myelodysplastic syndromes,” *Journal of Immunology*, 2000, 164:3689-97 – **Exhibit 19**
- Aruffo, S., Presentation of “Approaches to Immune Regulation” at BIO 2000 in Boston, Massachusetts, March 27, 2000 – **Exhibit 20**
- Basch, Ross S. et al., “Growth of Human Hematopoietic Cells in Immunodeficient Mice Conditioned with Cyclophosphamide and Busulfan,” *Stem Cells*, 1997, 15:314-23 – **Exhibit 21**
- Becker, J.C., Abstract and Presentation of “A multi-center, randomized, double-blind, placebo controlled study to evaluate the safety and preliminary clinical activity of multiple doses of CTLA4Ig and LEA29Y administration intravenously to subjects with rheumatoid arthritis,” presented at American College of Rheumatology Conference: “2001 Innovative Therapies in Autoimmune Diseases,” San Francisco, California, March 8, 2001 – **Exhibit 22**

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- Byrn, Randal A. et al., "Characterization of In Vitro Inhibition of Human Immunodeficiency Virus by Purified Recombinant CD4," *Journal of Virology*, 1989, 63:4370-5 – **Exhibit 29**
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- Dyson, P. J. et al., "Genes encoding ligands for deletion of V β 11 T cells cosegregate with mammary tumour virus genomes," *Nature*, 1991, 349:531-2 – **Exhibit 37**
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- Krishnamurti, Lashsmanan et al., "Bone Marrow Transplantation without Myeloablation for Sickle Cell Disease," *New England Journal of Medicine*, 2001, 344:68 – **Exhibit 58**
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- Larsen, Christian P., Presentation of "Costimulation blockade: progress toward clinical application" at Canadian Society of Transplantation Annual Scientific meeting in Mont Tremblant, Quebec, Canada, March 3-4, 2000 – **Exhibit 61**
- Larsen, Christian P. et al., Abstract of "Prolongation of Renal Allograft Survival with Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-IG Fusion Protein In Non-Human Primates," in *Transplantation*, 2000, 69:S123, #45 – **Exhibit 62**
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- Oaks, Martin K. et al., "A Native Soluble Form of CTLA-4," *Cellular Immunology*, 2000, 201:144-53 – **Exhibit 84**
- Owen, Ray D., "Immunogenetic Consequences of Vascular Anastomoses between bovine twins," *Science*, 1945, 102:400-1 – **Exhibit 85**
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- Ruedl, Christiane et al., "Phenotypic and functional characterization of CD11c⁺ dendritic cell population in mouse Peyer's patches," *European Journal of Immunology*, 1996, 26:1801-6 – **Exhibit 91**
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- Sfikakis, Peter P. et al., "CD28 Expression On T Cell Subsets In Vivo and CD28-Mediated T Cell Response In Vitro in Patients with Rheumatoid Arthritis," *Arthritis & Rheumatism*, 1995, 38:649-54 – **Exhibit 96**
- Shahinian, Arda et al., "Differential T Cell Costimulatory Requirements in CD28-Deficient Mice," *Science*, 1993, 261:609-12 – **Exhibit 97**
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- Srinivas, Nuggehally R. et al., "Assessment of Dose Proportionality, Absolute Bioavailability, and Immunogenicity Response of CTLA4Ig (BMS-188667), a Novel Immunosuppressive Agent, Following Subcutaneous and Intravenous Administration to Rats," *Pharmaceutical Research*, 1997, 14:911-6 – **Exhibit 104**
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- Sykes, Megan et al., "Induction of high levels of allogeneic hematopoietic reconstitution and donor-specific tolerance without myelosuppressive conditioning," *Nature Medicine*, 1997, 3:783-7 – **Exhibit 106**
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- Tomita, Yukihiko et al., "Role of Intrathymic Clonal Deletion and Peripheral Anergy in Transplantation Tolerance Induced by Bone Marrow Transplantation in Mice Conditioned with a Nonmyeloablative Regimen," *Journal of Immunology*, 1994, 153:1087-98 – **Exhibit 109**
- Turgeon, Nicole A. et al., "Viral Infection Abrogates CD8⁺ T-cell Deletion Induced by Costimulation Blockade," *Journal of Surgical Research*, 2000, 93:63-9 – **Exhibit 110**

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- Vermes, István et al., "A novel assay for apoptosis Flow cytometric detection of phosphatidylserine expression on early apoptotic cells using fluorescein labelled Annexin V," *Journal of Immunological Methods*, 1995, 184:39-51 – **Exhibit 112**
- Vermylen, C. et al., "Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium," *Bone Marrow Transplantation*, 1998, 22:1-6 – **Exhibit 113**
- Walters, Mark C. et al., "Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report," *Blood*, 2000, 95:1918-24 – **Exhibit 114**
- Warner, G. L. et al., Abstract and Presentation of "Bioactivity of BMS-188667 (CTLA4Ig) in Cynomolgus Monkeys," in Seattle, Washington, March 16-22, 1995 – **Exhibit 115**
- Webb, Louise M. C. et al., "Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2" *European Journal of Immunology*, 1996, 26:2320-8 – **Exhibit 116**
- Weinblatt, Michael E. et al., "A Trial of Etanercept, A Recombinant Tumor Necrosis Factor Receptor: Fc Fusion Protein, in Patients with Rheumatoid Arthritis Receiving Methotrexate," *New England Journal of Medicine*, 1999, 340:253-9 – **Exhibit 117**
- Weiner, R. et al., Abstract and Presentation of "Validation and PK Application of a Double Antibody Sandwich Enzyme Immunoassay For the Quantitation of Human CTLA4Ig Fusion Protein (BMS-188667) in Mouse Serum," November 6-10, 1994 – **Exhibit 118**
- Weiner, Russell et al., Abstract and Presentation of "Validation of an Enzyme Immunoassay for the Quantitation of Human CTLA4Ig Fusion Protein in Human Serum," in Miami, Florida, November 1995 – **Exhibit 119**
- Weiner, Russell, Abstract and Presentation of "Automation and Validation of An EIA For Quantitation of Human CTLA4Ig in Monkey Serum," in Miami, Florida, November 1995 – **Exhibit 120**

- Weiner, Russell S. et al., "A sensitive enzyme immunoassay for the quantitation of human CTLA4Ig fusion protein in mouse serum: pharmacokinetic application to optimizing cell line selection," *Journal of Pharmaceutical and Biomedical Analysis*, 1997, 15:571-579 – **Exhibit 121**
- Weiner, Russell S., Abstract and Presentation of "Industrial Perspectives of Primary Analytical Tools for Macromolecules- Principles and Applications with Examples" March 1, 2000 – **Exhibit 122**
- Wekerle, Thomas et al., "Extrathymic T Cell Deletion and Allogeneic Stem Cell Engraftment Induced with Costimulatory Blockade Is Followed by Central T Cell Tolerance," *Journal of Experimental Medicine*, 1998, 187:2037-44 – **Exhibit 123**
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- Wells, Andrew D. et al., "Following the Fate of Individual T Cells throughout Activation and Clonal Expansion," *Journal of Clinical Investigation*, 100:3173-83 – **Exhibit 125**
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- Whitmire, Jason K. et al., "CD40 Ligand-Deficient Mice Generate a Normal Primary Cytotoxic T-Lymphocyte Response but a Defective Humoral Response to a Viral Infection," *Journal of Virology*, 1996, 70:8375-81 – **Exhibit 127**
- Whitmire, Jason K. et al., "CD40-CD40 Ligand Costimulation is Required for Generating Antiviral CD4 T Cell Responses But Is Dispensable for CD8 T Cell Responses," *Journal of Immunology*, 1999, 163:3194-201 – **Exhibit 128**
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- Zarozinski, Christopher C. and Raymond M. Welsh, "Minimal Bystander Activation of CD8 T Cells during the Virus-induced Polyclonal T Cell Response," *Journal of Experimental Medicine*, 1997, 185:1629-39 – **Exhibit 136**

This statement should be considered because it is submitted before the mailing date of the first Office Action on the merits according to 37 C.F.R. §1.97(b)(3). In accordance with 37 C.F.R. §1.98(a)(2), copies of each document or other information listed on the enclosed Form 1449 are provided.

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the reference(s) are not "prior art." Moreover, Applicants do not represent that the

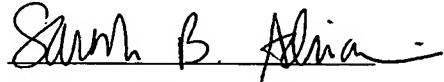
Christian P. Larsen, et al.
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references have been thoroughly reviewed or that any relevance of any portion of a reference is intended.

Consideration of the items listed is respectfully requested. Pursuant to the provisions of M.P.E.P. § 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 50-0306.

Respectfully submitted,



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FORM 1449*		Docket Number D0136NP/30436.58USU1	Application Number 10/057,288
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		Filing Date January 25, 2002	Group Art Unit 1646

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U.S. PATENT DOCUMENTS						
EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	4,603,102 (Exhibit 1)	07/29/86	Himmelmann et al.			06/26/85
	5,430,057 (Exhibit 2)	07/04/95	Andersson et al.			09/30/93
	5,434,131 (Exhibit 3)	07/18/95	Linsley et al.			05/26/93
	5,559,148 (Exhibit 4)	09/24/96	Andersson et al.			05/24/95
	5,637,481 (Exhibit 5)	06/10/97	Ledbetter et al.			09/13/93
	5,773,253 (Exhibit 6)	06/30/98	Linsley et al.			07/21/95
	5,844,095 (Exhibit 7)	12/01/98	Linsley et al.			01/18/95
	5,851,795 (Exhibit 8)	12/22/98	Linsley et al.			06/02/95
	5,876,692 (Exhibit 9)	03/02/99	Ildstad			01/17/97
	5,885,579 (Exhibit 10)	03/23/99	Linsley et al.			07/08/97
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	6,113,898 (Exhibit 13)	09/05/00	Anderson et al.			06/07/95
	6,217,867 B1 (Exhibit 14)	04/17/01	Ildstad			10/22/98

FOREIGN PATENT DOCUMENTS						
DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
					YES	NO
WO96/23071 (Exhibit 15)	08/01/96	PCT				X

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)		
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		Billingham, R. E. et al., "'Actively Acquired Tolerance' of Foreign Cells," <i>Nature</i> , 1953, 172:603-6 (Exhibit 25)	
		Bratton, Donna L. et al., "Appearance of Phosphotidylserine on Apoptotic Cells Requires Calcium-mediated Nonspecific Flip-Flop and Is Enhanced by Loss of the Aminophospholipid Translocase," <i>Journal of Biological Chemistry</i> , 1997, 272:26159-65 (Exhibit 26)	
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		Closse, Christéle et al., "Phosphatidylserine-related adhesion of human erythrocytes to vascular endothelium," <i>British Journal of Hematology</i> , 1999, 107:300-2 (Exhibit 32)	
		Craddock, Charles, "Nonmyeloablative stem cell transplants," <i>Current Opinion in Hematology</i> , 1999, 6:383-7 (Exhibit 33)	
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		Frasch, S. Courtney et al., "Regulation of Phospholipid Scramblase Activity during Apoptosis and Cell Activation by Protein Kinase C δ ," <i>Journal of Biological Chemistry</i> , 2000, 275:23065-73 (Exhibit 40)	
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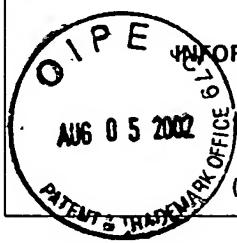
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		Larsen, Christian P., Presentation of "Costimulation blockade: Progress toward clinical application" at the American Society of Transplantation Meeting in Las Croabas, Puerto Rico, Jan. 13-17, 2000 (Exhibit 60)	
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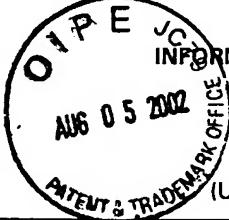
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 INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION <small>AUG 05 2002</small> <small>PATENT & TRADEMARK OFFICE</small> <small>USE several sheets if necessary</small>		Applicant Christian P. Larsen et al.	
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